Vulnerable Populations in *Safeguarding Children: Pediatric Medical Countermeasure Research*

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I. Introduction

Vulnerability is often understood to stem from a person's inability fully and independently to protect their own interests. Some individuals or groups that participate in human subjects research are vulnerable because they lack the capacity or have an impaired capacity for voluntary informed consent, or because of circumstances, such as severe illness or economic deprivation, that put them at increased risk of being exploited or unfairly taken advantage of in the research setting.[1]

Children are a vulnerable population because they lack the autonomy and decision making capacity to ethically and legally consent to participate in research and to understand and assume

[1] See the *Vulnerable Populations Background* module for a further discussion of vulnerability in the research setting. The module is available at www.bioethics.gov/education.

the risks of research, and because of inequalities of power between adults and children.[2] Children are also vulnerable in that unless we conduct pediatric research we will not be able to offer children safe and effective interventions. These vulnerabilities have given rise to additional protections for children participating in research that are described in U.S. federal regulations governing human subjects research.[3]

In its report, *Safeguarding Children: Pediatric Medical Countermeasure Research* (*Safeguarding Children*), the Presidential Commission for the Study of Bioethical Issues (Bioethics Commission) advised the U.S. government on the ethical considerations involved in evaluating and conducting pediatric medical countermeasure research both before a bioterrorism attack (pre-event) and after an attack (post-event). The Bioethics Commission's analysis included specific consideration of anthrax vaccine adsorbed (AVA), a vaccine that would be made available for post-event prophylaxis in the event of an anthrax attack.

The term medical countermeasure (MCM) has been defined in different ways. In *Safeguarding Children*, the Bioethics Commission considered it to include FDA-regulated products and interventions used in response to chemical, biological, radiological, and nuclear attacks.[4] Development of pediatric MCMs lags in comparison to MCMs for the adult population in part due to the challenges inherent to collecting data in pediatric populations.[5]

Pediatric MCM research presents ethical challenges in addition to those encountered in other areas of pediatric research. *Pre-event* MCM research is conducted in preparation for a potential future attack and generally involves testing an intervention with healthy participants. Because participants have not been exposed to the agent that the MCM is designed to protect against, pre-event MCM research offers no prospect of direct benefit to participants. Moreover, pre-event research generates knowledge that we might never have—and hope never to have—occasion to use.

Post-event MCM research involves participants who have been exposed to the agent and, in many cases, have already received the MCM as an intervention.[6] If an untested MCM (i.e., one not tested in children) is given to children in an emergency, post-event MCM research is

[2] Presidential Commission for the Study of Bioethical Issues. (2013, March). *Safeguarding Children: Pediatric Medical Countermeasure Research*. Washington, DC: PCSBI, p. 26. See also Kipnis, K. (2003). Seven vulnerabilities in the pediatric research subject. *Theoretical Medicine and Bioethics*, 24, 107-120.
[3] *Protection of Human Subjects, HHS*. 45 C.F.R. Part 46, Subpart D; *Protection of Human Subjects, FDA.* 21 C.F.R. Part 50, Subpart D.
[4] PCSBI, (2013, March), op cit, p.18.
[5] Letter from Secretary Kathleen Sibelius, Health and Human Services (HHS), to Amy Gutmann, Chair, Presidential Commission for the Study of Bioethical Issues (PCSBI). (2012, January 6), p. 1. Retrieved August 14, 2014, from http://bioethics.gov/node/633.
[6] In an emergency, in an effort to protect children, the U.S. government might distribute an intervention that is not yet approved by FDA, or has been tested only on adults. In these circumstances FDA can authorize the use of unapproved products using specific regulatory mechanisms. For further discussion of these mechanisms see PCSBI, (2013, March), op cit, pp. 97-102.

ethically imperative to safeguard the wellbeing of current and future children.[7] Even if some pre-event testing has taken place, post-event research is necessary to better understand the MCM. Because children enrolled in post-event research were exposed to the agent and given the MCM as a treatment, the research in which they participate carries lower risk (i.e., because the risk of taking the MCM is a risk of treatment, not research, the risks of research would be the risks of any additional procedures necessary to observe post-event safety), and could create the potential for direct benefit for participants (e.g., through monitoring and mitigating adverse events).[8] It also has the potential to create generalizable knowledge about participants' condition. However, post-event research generally will be conducted under stressful conditions in which it might be more difficult to implement certain ethical safeguards, such as informed parental permission and meaningful child assent.[9]

In *Safeguarding Children* the Bioethics Commission found that the tension between the need to protect all children to the extent possible in the event of a future attack and the need to protect children participating in research from which they do not stand to directly benefit "creates the central ethical challenge of pediatric MCM research."[10]

II. Learning Objectives

Students should be able to:

1. Understand why children are a vulnerable population and why special safeguards are needed to protect children as research participants.

2. Understand the differences between pre-event and post-event MCM research and the ethical challenges of research with children in each context.

3. Describe conditions under which pre-event MCM research with children is ethically permissible.

4. Understand the protections afforded to pediatric research participants in the federal regulations, particularly the minimal risk standard.

III. Background

A. Children as a Vulnerable Population

In the context of human subjects research, children as a class are vulnerable in two ways. First, children are vulnerable to being exploited or unfairly taken advantage of in the research setting.

[7] PCSBI, (2013, March), op cit, p. 89.
[8] PCSBI, (2013, March), op cit, p. 50.
[9] PCSBI, (2013, March), op cit, p. 92.
[10] PCSBI, (2013, March), op cit, p. 12.

Their vulnerability in this sense derives from the fact that children lack the developed cognitive capacities necessary to deliberate about and consent to participate in research, and are subject to legal and social expectations of deference to adult authority and imbalances of power between adults and children.[11]

Second, children are vulnerable to increased health risks because of a lack of adequate pediatric research and testing of medical interventions with pediatric populations. Children are not "small adults"; they differ from adults in the ways they process medicines, respond to interventions, and interact with their environment.[12] It is necessary to test interventions with pediatric research participants that will later be given to children.[13] Due to a lack of adequate testing with pediatric populations, physicians prescribing medications to children often operate without sufficient information accurately to estimate dosages, formulations, or treatment regimens for children.[14] Additionally, children might be uniquely vulnerable to particular health risks, making it important that research on interventions to ameliorate those risks be conducted with pediatric participants. For example, exposure to smallpox might affect children more than adults, since some adults will have been vaccinated and might retain residual immunity against the disease.[15]

It is imperative that pediatric research be conducted to ensure that children have access to medical interventions that are safe and effective, and pediatric research must adhere to ethical standards designed to provide additional safeguards to protect children. These safeguards include:

a. Parental permission: Because children cannot ethically or legally consent to participate in research, parents or guardians give or withhold permission to participate on their child's behalf, operating on their understanding of what is in their child's best interests.

b. Meaningful child assent: At different ages children have varying capacities to make decisions about their involvement in research, and to express meaningful assent or dissent to participation. Whenever developmentally appropriate, their assent should be solicited, and, if applicable, their dissent respected.

[11] Kipnis, K. (2003). Seven vulnerabilities in the pediatric research subject. *Theoretical Medicine and Bioethics*, 24, 107-120.
[12] Klassen, T.P. et al. (2008). Children are not just small adults: The urgent need for high-quality trial evidence in children. *PLoS Medicine*, 5(8), 1180-1182.
[13] The necessity for testing interventions that will be used for children with pediatric populations applies also to non-medical interventions (e.g., educational or psychological interventions).
[14] PCSBI, (2013, March), op cit, p. 22. See also Klassen, T.P. et al. (2008). Children are not just small adults: The urgent need for high-quality trial evidence in children. *PLoS Medicine*, 5(8), 1180-1182.
[15] Routine vaccination against smallpox ended in the United States in 1972. For more details see Cieslak, T.J., and F.M. Henretig (2003). Ring-a-ring-a-roses: Bioterrorism and its peculiar relevance to pediatrics. *Current Opinion in Pediatrics*, 15, p. 108.

c. Limits on the degree of permissible research-related risk: A risk ceiling on pediatric research ensures that pediatric research participants are not exposed to an exploitative level of risk to benefit others in society.[16]

In its 1977 report, *Research Involving Children*, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research clarified what became the guiding principle of pediatric research in the United States and around the world: pediatric research generally should be allowed only when it exposes children to minimal risk (i.e., a level of risk in which the degree and likelihood of harm is no greater than that faced by a healthy child in daily life or at a routine medical examination), unless there is a prospect of direct benefit to participants. The importance of a risk ceiling for pediatric research stems directly from the vulnerability of children:

> Except in extraordinary circumstances, asking children to take on greater risk in research when they do not stand to benefit directly pushes the bounds of ethical acceptability because children do not have the legal or ethical capacity to consent, and society has a duty to protect children from risk of harm to which they cannot consent.[17]

Limits on the level and types of research risks a child can be asked to assume are key to protecting children as a vulnerable population and as such are central to the federal regulations for research involving children.

B. Regulations for Pediatric Research

Federal regulations for the protection of human subjects in research are contained in Subpart D of Department of Health and Human Services (HHS) regulations at 45 Code of Federal Regulations (C.F.R.) Part 46 and FDA regulations at 21 C.F.R. Part 50.[18] Subpart A of 45 C.F.R. Part 46, referred to as the Common Rule, governs research with adult participants. Pediatric research regulations are specified in Subpart D. Subpart D specifies stringent protections for children in research that apply in addition to those that govern research with adults. These regulations provide the conditions under which local institutional review boards (IRBs) can review and approve research involving children. Research categories subject to local IRB review are:

a. Research that does not involve greater than minimal risk (45 C.F.R.§ 46.404);

[16] PCSBI, (2013, March), op cit, p. 28.
[17] PCSBI, (2013, March), op cit, p. 24.
[18] The language of the two sets of regulations is substantively identical. The Bioethics Commission refers only to HHS regulations in this module, although the discussion encompasses the provisions of Subpart D as codified by both HHS and FDA.

b. Research that involves greater than minimal risk but presents the prospect of direct benefit to participants (45 C.F.R.§ 46.405); or

c. Research that involves a minor increase over minimal risk with no prospect of direct benefit to participants, but is likely to yield generalizable knowledge about the participant's condition (45 C.F.R.§ 46.406).[19]

Research that falls outside of these categories, such as research with healthy children that involves more than minimal risk and does not offer the prospect of direct benefit, must be evaluated and approved at the national level (45 C.F.R.§ 46.407). In order for research to be approved at this level, the Secretary of HHS, in consultation with an independent panel of experts, must determine that the protocol under review meets all of the following conditions:

a. The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;

b. The research will be conducted in accordance with sound ethical principles; and

c. Adequate provisions are made for permission of parents and guardians and meaningful child assent (or affirmative agreement) of children.[20]

In *Safeguarding Children* the Bioethics Commission recommended that pre-event pediatric MCM research should be conducted only with a minimal level of research risk except under extraordinary circumstances. However, barriers to minimal risk research, discussed below, make it likely that some pre-event pediatric MCM research will pose greater than minimal risk to participants and therefore will be approvable only under section 407 of the regulations.

The following table provides examples of conditions and procedures that the Bioethics Commission identified as minimal risk or a minor increase over minimal risk.

	Minimal risk	**Minor increase over minimal risk**
Conditions	Redness or moderate soreness at injection site	Missing a few days of school due to temporary low fever or malaise
Procedures	Drawing blood	Skin biopsy or chest X-ray

Source: Presidential Commission for the Study of Bioethical Issues (PCSBI). (2013, March). *Safeguarding Children: Pediatric Medical Countermeasure Research*. Washington, DC: PCSBI, p. 68.

[19] PCSBI, (2013, March), op cit, pp. 37-39.
[20] PCSBI, (2013, March), op cit, p. 44.

The Bioethics Commission recommended an ethical framework that clarifies when proposed research presents a "reasonable opportunity" to address a "serious problem" affecting children; specifies conditions necessary to determine whether the research would be conducted in accordance with "sound ethical principles"; and reiterates the importance of informed parental permission and meaningful child assent.[21] The ethical framework is summarized in the table below.

An Ethical Framework to Guide National-Level Review of Pediatric Medical Countermeasure Research under 45 C.F.R § 46.407 and/or 21 C.F.R. § 50.54

1. Does the research present a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem that could affect the health or welfare of children?

- A. Serious problem, as judged by:
  - i. Consequences of exposure
  - ii. Likelihood (or threat) of exposure
  - iii. "Vital importance"
- B. Reasonable opportunity

2. Will the research be conducted in accordance with sound ethical principles?

- A. Ethical threshold of acceptable risk and adequate protection from harm
- B. Ethical research design
  - i. Scientific necessity
  - ii. Research plan
    - a. Scientific validity
    - b. Small trials and age de-escalation
    - c. Appropriate monitoring
    - d. Proper planning for post-event research
  - iii. Prior adult testing to minimize risk to children
  - iv. Sufficient benefit over alternatives
  - v. Fair subject selection
- C. Post-trial requirements to ensure ethical treatment of children and their families
  - i. Distribution protocol for all children tested or assured
  - ii. Compensation for research-related injury
- D. Community engagement in pre-event research
- E. Transparency and accountability

3. Are adequate provisions made for soliciting the permission of parents or guardians and the meaningful assent of children?

Source: Presidential Commission for the Study of Bioethical Issues (PCSBI). (2013, March). *Safeguarding Children: Pediatric Medical Countermeasure Research*. Washington, DC: PCSBI, p. 138.

[21] PCSBI, (2013, March), op cit, p. 62.

C. Scientific, Practical, and Ethical Challenges of Pediatric MCM Research

1. Pre-event Research

Absent exceptional circumstances, general pediatric research posing more than a minimal risk to participants is ethically permissible only if (i) it offers the prospect of direct benefit to participants, or (ii) it is likely to generate important knowledge about the participants' condition.[22] Pre-event pediatric MCM research generally fails to meet these conditions. Pre-event MCM research typically involves testing an intervention with healthy participants who have not been exposed to the agent for which the intervention is designed; it therefore offers no prospect of direct benefit to participants. Additionally, pre-event MCM research relies on participants who have not been exposed to the agent in question, so they do not have a condition about which the research could generate important knowledge. Moreover, the research would produce results that we expect and hope never to have to use.[23]

Given these features of pre-event MCM research, the Bioethics Commission found that there are two ethically appropriate options for conducting such research with children:

a. Ensure that the research poses only a minimal risk to participants. Prior testing of the intervention on adults can help identify, understand, and characterize the risks of the intervention. Age de-escalation trials should be employed when possible. For example, if it is possible to design and conduct informative minimal risk research with the youngest adults (e.g., 18 years of age), the same research design—modified in accordance with information obtained from prior research—could form the basis of a study that would similarly be minimal risk with the oldest children (e.g., 16 and 17 years of age), and so on as a stepwise series of minimal risk protocols through to the youngest group of children. Cautious and scientifically sound age de-escalation trials provide additional protection to the most vulnerable members of the group (the youngest children) by beginning with those who are less vulnerable (the youngest adults).[24]

b. If minimal risk research is impossible, the Bioethics Commission recommended that proposed research expose children to no more than a minor increase over minimal risk, a level that is still very limited and poses no substantial risk to health or wellbeing.[25] Pre-event pediatric MCM research that poses no more than a minor increase over minimal risk can proceed to national-level review under 45 C.F.R.§ 46.407 and reviewers should apply the Bioethics Commission's recommended framework.

[22] PCSBI, (2013, March), op cit, p. 49.
[23] PCSBI, (2013, March), op cit, p. 51.
[24] PCSBI, (2013, March), op cit, p. 52.
[25] PCSBI, (2013, March), op cit, p. 59. Examples of risks at this level include those associated with a temporary low fever, a skin biopsy, or X-ray. PCSBI, (2013, March), op cit, p. 68

Although not explicitly dictated by Subpart D, the Bioethics Commission found that pediatric research posing more than a minor increase over minimal risk is not permissible in the MCM context. This impermissibility reflects the unique characteristics of pre-event MCM research, namely that it offers no prospect of direct benefit to participants, involves research on a hypothetical condition with an undefined (and possibly unknowable) likelihood of occurring, and generates knowledge that we hope never to have to use.[26] In addition, because children cannot ethically or legally consent to assume the risks of research, and because they are vulnerable individuals who need to be protected from undue risks undertaken for the benefit of others, the Bioethics Commission considered this risk ceiling to be consistent with established ethical principles for pediatric research.[27]

2. Post-event Research

The ethical considerations of pediatric post-event MCM research—that which is conducted after a bioterrorism attack occurs—differ from those of pre-event research. Even if pre-event testing of the MCM has been done, it, by definition, will be the minimum necessary to establish basic dosing and safety. Post-event research is necessary to gather additional safety data about an intervention that is administered to children in the absence of existing FDA approval. Gathering these safety data in a post-event situation is ethically required to safeguard the wellbeing of current and future children.[28] In post-event research, participants are likely to have been exposed to the agent, which means that the research might yield important information about their condition (approvable under section 406), or might offer the prospect of direct benefit to participants (e.g., monitoring or mitigating adverse events) (approvable under section 405). In post-event research participants have already received the intervention as a form of treatment. Therefore, the only risks of research are the risks related to observation and follow up (e.g., blood draws, physical examinations, or surveys). Such observational research might be minimal risk, thus approvable under section 404.[29]

The emergency circumstances in which post-event research takes place might make it more difficult to obtain adequate parental permission and child assent. The Bioethics Commission recommended that researchers and IRBs ensure that special measures are taken to provide essential information about pediatric post-event MCM research to parents and, where appropriate, to participants.[30]

[26] PCSBI, (2013, March), op cit, pp.13, 51.
[27] PCSBI, (2013, March), op cit, p. 50.
[28] PCSBI, (2013, March), op cit, p. 89.
[29] PCSBI, (2013, March), op cit, p. 89.
[30] PCSBI, (2013, March), op cit, p. 92.

D. Bioethics Commission Recommendations

Each of the Bioethics Commission's recommendations in *Safeguarding Children* emphasizes the additional safeguards needed to protect children participating in MCM research.

Recommendations 1, 2, 3, and 4 concern scenarios in which it is ethically permissible to conduct pre-event pediatric MCM research, focusing extensively on the permissible level of risk:

> **Recommendation 1: Pre-event Pediatric Medical Countermeasure Research Risk Limited to Minimal Except under Extraordinary Circumstances**
>
> **Pre-event pediatric medical countermeasure testing should be conducted with a research design posing only a minimal level of research risk except under extraordinary circumstances. If pre-event pediatric medical countermeasure research cannot be conducted as a minimal risk study, research that exposes children to no more than a minor increase over minimal risk—a level that is still very limited and poses no substantial risk to health or wellbeing—should proceed to a national-level review under Department of Health and Human Services regulations at 45 C.F.R. § 46.407 and/or U.S. Food and Drug Administration regulations at 21 C.F.R. § 50.54.**[31]
>
> **Recommendation 2: Risk in Pre-event Pediatric Medical Countermeasure Research**
>
> **Before beginning pre-event medical countermeasure studies with children, ethically sound modeling, testing with animals, and testing with the youngest adults must be completed to identify, understand, and characterize research risks. If pediatric research is determined to be minimal risk and is to be conducted, progressive age de-escalation should be employed whenever possible from the oldest age group of children to the youngest group necessary to provide additional protection to the youngest and most vulnerable children, and to ensure that data from an older age group can inform the research design and the estimate of risk level for the next younger age group.**[32]
>
> **Recommendation 3: Pre-conditions to National-Level Review of Pre-event Pediatric Medical Countermeasure Research**
>
> **Pre-event pediatric medical countermeasure research may proceed to national-level review under Department of Health and Human Services regulations at 45 C.F.R. § 46.407 and/or U.S. Food and Drug Administration regulations at 21 C.F.R. § 50.54 only when researchers have demonstrated and reviewers concur that a minimal risk study is impossible and the proposed study poses no more than a minor increase over minimal risk to research participants. In part because of the inherent uncertainty of a bioterrorism attack, pre-event pediatric medical countermeasure research posing greater than a minor increase over minimal risk should not be approved under 45 C.F.R. § 46.407 or 21 C.F.R. § 50.54.**[33]

[31] PCSBI, (2013, March), op cit, p. 56.
[32] PCSBI, (2013, March), op cit, p. 56.
[33] PCSBI, (2013, March), op cit, p. 61.

> **Recommendation 4: Ethical Framework for National-Level Review of Pre-event Pediatric Medical Countermeasure Research [excerpt]**
>
> **To ensure the thoroughness and ethical rigor of national-level review, reviewers should apply the Bioethics Commission's recommended ethical framework for reviewing pre-event pediatric medical countermeasure research that poses greater than minimal risk, but no more than a minor increase over minimal risk, under Department of Health and Human Services regulations at 45 C.F.R. § 46.407 and/or U.S. Food and Drug Administration regulations at 21 C.F.R. § 50.54. A proposed protocol must meet the requirements of the framework outlined in this report to be approved.**[34]

The Bioethics Commission's ethical framework clarifies the circumstances in which proposed research presents a "reasonable opportunity" to address a "serious problem" affecting the health or wellbeing of children, and specifies a rigorous set of conditions to determine whether the research would be conducted in accordance with "sound ethical principles." It also reiterates the importance of informed parental permission and meaningful child assent.

Recommendations 5 and 6 concern the safeguards that should be in place to protect children participating in post-event MCM research:

> **Recommendation 5: Post-event Pediatric Medical Countermeasure Research**
>
> **Post-event research should be planned in advance and conducted when untested medical countermeasures are administered to children in an emergency or when limited pre-event medical countermeasure studies have already occurred. Institutional review boards must be cognizant of the exigencies imposed upon research under emergency conditions, and when reviewing post-event medical countermeasure research proposals, ensure that adequate processes are in place for informed parental permission and meaningful child assent. Institutional review boards must also ensure that the research design is scientifically sound, children enrolled in research have access to the best available care, adequate plans are in place to treat or compensate children injured by research, and provisions are made to engage communities throughout the course of research.**[35]
>
> **Recommendation 6: Regulatory Mechanisms for Post-event Pediatric Medical Countermeasure Research and Distribution**
>
> **When there are no data on the administration of a medical countermeasure to children and it will be provided to children in an emergency, the medical countermeasure should be provided under a treatment investigational new drug application (IND) to ensure that rigorous pediatric research protections apply to safeguard those children who receive the medical countermeasure. When a medical countermeasure is distributed broadly to children using a treatment IND, it is essential that the U.S. government also conduct a concurrent small-scale study under an investigator IND to obtain data that can potentially be used to support an**

[34] PCSBI, (2013, March), op cit, p. 87.
[35] PCSBI, (2013, March), op cit, p. 97.

emergency use authorization for pediatric use of the medical countermeasure in a future event. To expedite post-event research and ensure the availability of appropriate medical countermeasures for children, a pre-IND consultation and approval should be put in place before an event.[36]

IV. Reading

For the purposes of discussion, students should download and read the following Bioethics Commission materials (reports are available for download on the Bioethics Commission's website at www.bioethics.gov under "Projects"):

Safeguarding Children, pp. 12-15 ("Introduction").

Safeguarding Children, pp. 22-36 ("Current Ethical and Regulatory Framework for Pediatric Research").

Safeguarding Children, pp. 48-61 ("Ethical Considerations for Pediatric Medical Countermeasure Research").

Safeguarding Children, pp. 89-92 ("Post-event Studies").

V. Discussion Questions

The following questions are based on the information provided above and through the indicated reading and are intended to reinforce important aspects of research with vulnerable populations highlighted in *Safeguarding Children*. Important points are noted with each question to help the instructor guide a group discussion. The "Additional Resources" section will be helpful in answering these questions.

1. What does it mean to describe children as a "vulnerable population"?

Starting points for discussion:

a. Children are vulnerable because they lack the developed cognitive capacity to decide for themselves whether to participate in research and assume the risks of doing so.

b. Children are expected to defer to adult authority and power, which makes them vulnerable to exploitation by adults.

c. Children are vulnerable when social or economic disadvantage, medical need, or urgency makes them or their parents more willing to accept research risks.

[36] PCSBI, (2013, March), op cit, pp. 101-102.

d. Children are vulnerable when lack of research with pediatric participants exposes them to the unknown risks of imprecise dosages, formulations, or treatment regimens.

e. Children might be more vulnerable to particular health risks than adults (e.g., adults are more likely than children to have residual immunity against smallpox).

2. Why is it important for research, including MCM research, to be conducted with pediatric populations?

Starting points for discussion:

a. Children differ from adults in the ways they process medicines, respond to interventions, and interact with their environment. Pediatric research is essential to ensure that children have access to therapies that are safe and effective in the event of a bioterrorism attack.

b. Children's physiology changes constantly as they develop. Research is required to determine appropriate interventions and dosages for different stages of physiological development.

c. Some diseases occur mostly during childhood. Treatments for these diseases would need to be tested with affected children to assess safety and effectiveness.

3. What is child assent and how do parental permission and child assent protect children as a vulnerable population?

Starting points for discussion:

a. While children are ethically and legally incapable of giving informed consent, they have varying capacities to make informed choices and to express their preferences.

b. Parental permission requires that parents or guardians act in accordance with their understanding of what is in their child's best interests.

c. Seeking meaningful child assent demonstrates respect for children as persons and reflects their (limited) capacity for self-determination and developing autonomy. Child assent does not have the ethical or legal standing of informed consent, but ensures that children who are developing the capacity for autonomous decision making are included in the decision making process.

d. In the case of research that does not offer a prospect of direct benefit to participants, a child who meaningfully dissents, or does not agree to participate, should not participate. Parental permission cannot override a child's sustained, meaningful dissent in this case.[37] Respecting a child's meaningful and developmentally appropriate dissent helps to ameliorate some of a child's vulnerability that is due to the expectation of deference to adults.

4. Why is it important to limit the degree of permissible risk in pediatric research? Under what conditions could pediatric pre-event MCM research be considered minimal risk?

Starting points for discussion:

a. Limits on acceptable risk are one of the safeguards for protecting children participating in research in light of their inherent vulnerability.

b. Children cannot ethically or legally consent to participate in research, and so cannot consent to assume the risks of participation. Risk limits are particularly important when the benefits of the research will accrue to others, but not research participants; they ensure that child research participants are not exposed to an exploitative level of risk for the sake of others in society.

c. Pre-event MCM research could be considered minimal risk when it follows extensive testing in adults to identify, understand, and minimize the risks of research. Once these risks are understood, data from minimal risk research with the youngest adults (e.g., 18 years of age) might be used as the basis of a study that would be similarly minimal risk for the oldest children (e.g., 16 and 17 years of age). To the extent that it is possible to infer minimal risk from research with the previous age cohort, "age de-escalation" would continue as a stepwise series of minimal risk protocols through to the youngest children.

5. What features of post-event MCM research raise ethical concerns for pediatric research participants? What can be done to ensure that children participating in post-event MCM research are adequately protected?

Starting points for discussion:

a. Post-event research occurs in emergency circumstances, for example immediately following a bioterrorism attack when an MCM has already been administered to protect children and adults. Under these circumstances, researchers might have less than optimal time to engage with parents and children, who might be

[37] For further discussion of child assent and dissent see Wendler, D. (2006). Assent in paediatric research: Theoretical and practical considerations. *Journal of Medical Ethics*, 32(4), 229-234.

experiencing uncertainty, confusion, and fear. These circumstances might strain the process of obtaining informed parental permission and meaningful child assent.

b. Researchers should design consent forms for pediatric post-event MCM research to be as simple and straightforward as possible while still providing the information necessary for an informed decision.

c. Researchers can engage in pre-approval consultations with IRBs to ensure that research protocols, including informed consent procedures, are planned as much as possible in advance of an attack; IRBs can ensure that pediatric post-event research protocols are held to the same high standards of ethical conduct as research carried out under non-emergency circumstances.

VI. Problem-Based Learning

Scenario A. *Authorities responsible for emergency preparedness release a plan for responding to a bioterrorism attack. According to the plan, children and adults who have been exposed to the agent would receive a vaccine that has undergone testing in adults only. Because no pre-event studies of the vaccine have been conducted with children younger than 18 years, a proportion of children who receive the vaccine would also be enrolled in a post-event active surveillance trial to collect baseline data about the vaccine's effects in the pediatric population.*

The following additional readings will be useful in considering this scenario:

> *Safeguarding Children*, pp. 97-101 ("Authorizing Distribution of Unapproved Drugs in an Emergency").

1. Why is the enrollment of pediatric research participants in post-event research ethically distinct from pre-event research with pediatric participants?

Starting points for discussion:

a. Unlike pre-event MCM research, a post-event surveillance trial might offer the prospect of direct benefit to research participants (e.g., monitoring and mitigating adverse events), and is likely to generate information that will benefit all children who have been exposed to the agent.

b. A post-event surveillance trial involving monitoring and assessment might expose research subjects to only minimal risk because the study would likely include only minimal risk procedures such as physical examination, blood draws, and surveys. Since participants in post-event research have already received the untested or

minimally tested MCM as a treatment for exposure, the risk of taking the MCM is a risk of treatment, not research; the risks of research would be the risks of any additional procedures necessary to observe post-event safety.

2. What protections are necessary when the MCM given to children has not undergone pre-event pediatric testing? What ethical principles support giving children an untested MCM?

Starting points for discussion:

a. Children can be given an untested MCM under an investigational new drug application (IND) (for more information on INDs see the suggested reading for this scenario). A treatment IND allows for the use of a promising experimental drug or intervention in an emergency situation provided that:

   i. The persons to be treated have a serious or life-threatening disease or condition.
   ii. There is no comparable or satisfactory alternative therapy.
   iii. The potential benefits of the intervention justify the potential risks, and the potential risks are not unreasonable in the context of the disease or condition to be treated.
   iv. Providing the intervention will not interfere with clinical investigations or compromise the development of expanded access use.

b. Distributing an untested MCM under a treatment IND ensures that rigorous pediatric research protections apply to all children who receive the MCM, including IRB review and documented parental permission.

c. An investigator IND also should be approved to study the effects of the MCM in a subset of children who received it. This research is ethically required because it generates important safety and effectiveness data necessary to learn about how the MCM treats children who have been exposed and safeguard the wellbeing of current and future children.

d. The ethical principles that support giving children an untested MCM in the event of an attack include:

   i. Beneficence, which requires that when an existing MCM is expected to provide benefit, it should be made widely available, allowing parents to accept the MCM for their children if they choose.
   ii. Respect for persons, which requires that children be given rigorous pediatric research protections under a treatment IND.

Scenario B. *As part of a nationwide emergency preparedness plan, public health officials and researchers want to conduct a pre-event trial with pediatric participants of a vaccine to protect against plague. The potential risks of participating in the vaccine trial cannot be considered minimal for children.*[38]

The following additional reading from *Safeguarding Children* might be useful in considering this scenario:

Safeguarding Children, pp. 61-87 ("Specifying a Framework").

1. Under which federal regulations could this trial be approved? What protections for children do the regulations provide?

Starting points for discussion:

a. Pre-event research posing more than minimal risk can be approved only after a national review under 45 C.F.R. § 46.407. Per the Bioethics Commission's framework specifying section 407's requirements, this research is ethically permissible only if it poses risks that are no more than a minor increase over minimal, because the likelihood of a terror attack necessitating the use of the vaccine as an MCM is unknown or unknowable.

b. National-level review ensures that the research will be conducted in accordance with sound ethical principles, which, as specified by the Bioethics Commission, include an ethical research design, ethical treatment of children and their families after the trial, and an adequate informed consent process.

c. Because children cannot ethically and legally consent to assume the risks of research, the minor increase over minimal risk threshold protects them from undue risks undertaken for the benefit of others. It also protects them from assuming risks when there is no certainty regarding the likelihood of a bioterrorism attack.

d. National-level review ensures that the risks are justified given the seriousness of the problem and the opportunity presented by the research to address that problem.

2. What elements of the informed consent process are particularly important for protecting children (as a vulnerable group) when participating in this research?

[38] Cieslak, T.J., and F.M. Henretig (2003). Ring-a-ring-a-roses: Bioterrorism and its peculiar relevance to pediatrics. *Current Opinion in Pediatrics*, 15, 107-111.

Starting points for discussion:

a. Whatever level of developing autonomy children have must be respected and they must be given the opportunity to choose to participate to the extent that they are able. Children who meaningfully dissent or who do not agree to participate should not participate. Parental permission cannot override sustained meaningful dissent, except when the research offers a prospect of direct benefit to participants that is unavailable outside of the research context.[39]

b. The Bioethics Commission noted that for pediatric MCM research that involves greater than minimal risk and no prospect of direct benefit consent should be obtained by an independent person with expertise in developmentally appropriate child assent procedures.[40]

c. Researchers must ensure that potential participants, and parents, do not have a misperception of a prospect of direct benefit from the research. Informational materials must effectively communicate complex concepts including information about national security, the uncertainty of an attack, and the public health requirements for the MCM under investigation.

3. What ethical considerations should researchers address in selecting participants for this trial?

Starting points for discussion:

a. Fair subject selection is a necessary condition of ethical research, and is an important safeguard in pediatric research because all children are vulnerable.

b. The ethical principles of beneficence and justice require that the selection of participants be fair, minimize risks to and enhance benefits for participants, and fairly distribute research risks and benefits.

c. Researchers might consider whether potential child participants are burdened by multi-faceted vulnerabilities, such as cognitive or physical disabilities, or who are institutionalized or wards of the state. [41]

[39] *Protection of Human Subjects, HHS*. 45 C.F.R. § 46.408(a). In addition, the IRB could waive the assent requirement under circumstances in which consent may be waived under 45 C.F.R. §46.116, General requirements of informed consent.
[40] PCSBI, (2013, March), op cit, p. 85.
[41] See the *Vulnerable Populations: Background* module for further discussion of protecting children and other vulnerable groups in research. The module is available at www.bioethics.gov/education.

d. Researchers might consider whether children who participate in the research are at least as likely to benefit from the results of the proposed study as children who do not participate. Populations who meet this standard might be determined by considering:

    i. Potential to benefit: Children living in urban areas and families of first responders might be at greater risk of future exposure and so might be more likely to benefit from the results of pediatric MCM research in the event of an exposure.
    ii. Understanding of consequences of participation: Children of parents who are particularly well informed about the purpose and limits of pediatric MCM research—such as MCM researchers or policy makers—might be better equipped to understand the consequences of participation.

Scenario C. *A group of children have participated in pre-event MCM research that involved vaccination against an agent likely to be used in a terror attack. Two years later, there is an attack in a major city and the vaccine, which was shown to be effective, is in short supply. Emergency response officials propose that the children who participated in the study should not be eligible to receive the vaccine because they might have some residual protective immunity from participating in the original study.*

The following additional reading from *Safeguarding Children* might be useful in considering this scenario:

> *Safeguarding Children*, pp. 74-76 ("Post-trial Requirements to Ensure Ethical Treatment of Children and Their Families," and "Distribution Protocol for All Children Tested or Assured").

1. Is the proposal of the emergency response officials ethically justified? Explain your answer in terms of ethical principles.

Starting points for discussion:

a. The principle of justice requires that interventions shown to be effective be distributed equitably to all exposed children in the event that they are needed. Not giving children who participated in research access to the vaccine in an emergency situation would unfairly penalize them for their participation.

b. Pre-event MCM research with children is ethically justified based on its potential future benefit to children as a class. The principle of beneficence guides the assessment of risks and benefits in research, and ensures that the potential benefits of the research justify the risks inherent to participating. In order for the research

to be justified, the benefits of the research must be assured for all children, through a documented plan for the wide and equitable distribution of the intervention to all children who need it in the event of an attack.

2. **What mechanisms might be available to ensure a just distribution of limited vaccine supplies?**

   Starting points for discussion:

   a. Researchers and government officials should use existing plans that have been shown to be equitable and effective for the distribution of MCMs in the event of an emergency as models for the distribution of an intervention to children. Collaboration with emergency preparedness coordinators in affected communities is important to avoid redundant expenditure of resources.

   b. To the extent possible, emergency distribution plans should include provision for adequate quantities of the MCM.

   c. Officials should ensure that additional factors that make children vulnerable, such as age or poverty, do not determine how the vaccine is distributed in the affected population.

VII. Exercises

Exercise 1. *Review the following sections of* Safeguarding Children *and address the questions below.*

Safeguarding Children, pp. 127-131 (Appendix II: Summary of Pediatric Research Protocols Reviewed under 45 C.F.R. § 46.407 and/or 21 C.F.R. § 50.54 (1991-2012)).

Safeguarding Children, p. 128 (Hyperglycemic and Euglycemic-Hyperinsulinemic Clamp Procedure study).

1. **What reasons have been given for approving pediatric research protocols under section 407? Based on the reasons for approval, what language about the benefits of participation in these protocols do you think should have been included in the parental permission information?**

2. **Based on the available information about the Hyperglycemic and Euglycemic-Hyperinsulinemic Clamp Procedure study, do you agree or disagree with the IRB's initial assessment that the study "was no more dangerous than playing actively on sidewalks and streets"?**

3. **In this case, the government halted the study. In the case of pre-event pediatric MCM research, do you think such an action could be justified? Why or why not?**

4. **The study was ultimately approved under section 406 on the grounds that the participants at risk of developing Type 2 diabetes had a condition about which the research would generate important knowledge. What ethical considerations might this approval raise?**

Exercise 2. *Design a slide show that could be used in the event of an anthrax attack to educate communities about proposed post-event research with children who have been exposed and given an untested MCM for therapeutic reasons (e.g., AVA for post-event prophylaxis).*

You can read more about community engagement here:

> *Safeguarding Children*, pp. 95-97 ("Community Engagement in Post-event Research").

1. **What information would you need to provide in the presentation?**

2. **How might the circumstances of an attack influence the way you present the information?**

3. **Which stakeholders would it be most important to reach in these circumstances? How would you reach out to them?**

VIII. Glossary of Terms

Anthrax vaccine adsorbed (AVA): An FDA-approved human anthrax vaccine approved for pre-exposure use in those 18-65 years of age who are at high risk of exposure to anthrax.

Investigational new drug application (IND): An application submitted to FDA before studying a drug or biologic in humans.

> An *investigator IND* (used most commonly in research involving interventions) is submitted by a researcher who initiates and conducts an investigation of the investigational new drug.
>
> A *treatment IND* allows for the use of a promising experimental drug in the treatment of patients not enrolled in a clinical trial while the final clinical work and FDA review take place.

Medical countermeasure (MCM): FDA-regulated products and interventions used in response to chemical, biological, radiological, and nuclear attacks.

Minimal risk: Defined by the Code of Federal Regulations as "the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons" (45 C.F.R. §46.303), and generally understood to mean the degree of risk encountered in the daily life of a healthy individual living in a safe environment or the risk to which a healthy individual is exposed during a routine examination.

Minor increase over minimal risk: A level of risk that is a narrow expansion over minimal risk, but entailing no significant threat to an individual's health or wellbeing.

Vulnerable populations: Groups of individuals who are potentially unable to exercise control over how their interests are represented and pursued.

IX. Additional Resources

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Kopelman, L.M. (2004). What conditions justify risky nontherapeutic or "no benefit" pediatric studies: A sliding scale analysis. *Journal of Law, Medicine, & Ethics*, 32(4), 749-758.

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